

Quantitative Clinical Pharmacology Tools to Support Generic Drug Development: Regulatory Expectations and Case Examples

Advancing Generic Drug Development (AGDD): Leveraging Model-Integrated Evidence (MIE) in the Development & Approval of Generic Drugs – August 27, 2026

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Outline

- Quantitative clinical pharmacology (QCP) tools in generic drug development
- Population pharmacokinetic (PopPK) modeling approaches to support pre-ANDA submissions and ANDA approvals
- Dose-scale analysis to support ANDA approval

QCP Applications in Generic Drug Development



Category	BE Study Topic/Challenge	QCP Tools/Approaches
Alternative PK study designs	- Large number of subjects (e.g., parallel design, HVD with long half-life) - Recruitment challenges of patient populations (e.g., orphan drugs, ophthalmic drugs, sensitive patient populations)	- Adaptive design - MIE/VBE
	Long study duration (e.g., LAIs, long half-life drugs, steady-state design)	- Repeated crossover design (RRTT/TTRR) - Crossover with incomplete washout - Switch PK study - MIE/VBE
	Sparse PK sampling (e.g., LAIs, ophthalmic drugs, special populations)	MIE/VBE
	Reference standard is discontinued	PK BE bridging using alternative reference standard
	Low post-dose concentration relative to endogenous baseline levels	Alternative dose, study population, or pre-treatment
Study design and BE guidance clarifications	Dose scale analysis for PD BE study	Emax model development, validation, assessment
	Comparative clinical endpoint BE study	Dose and endpoint selection, sample size estimation
	PK sampling scheme and washout period	Optimal design, guidance, model-based methods
	Endogenous baseline correction method	Baseline patterns, sensitivity for BE, guidance/practice
	BE approach for NTI drugs	NTI drug assessment including PK/PD analysis
	Missing samples and data imputation	Model-based methods, sensitivity analysis, optimal design
	Assessment of steady-state attainment in PK studies	Statistical analysis, model-based methods
	Dose scale analysis	Emax model development and validation
Alternative BE metrics	Alternative partial AUC metrics	PK/PD analysis
	Switch PK study	Alternative BE limits based on MIE
	Drugs with long half-life	Suitability of AUC truncation
Statistical analysis and BE assessment	Justification in deviations in PK profiles (e.g. Tmax, Tlag, multiple peaks)	PK/PD analysis
	Impact of covariates (e.g., parallel design)	Covariate analysis in BE studies
	Unbalanced data after data exclusion	Data imputation, statistical analysis, sensitivity analysis
	Patient BE study with different doses	BE statistical analysis
	Outlier data (e.g., 'statistical outliers')	Data exclusion criteria, evaluation of model bias

Case Study #1: PopPK Model-Based Correction for Drug Carryover



Study Design

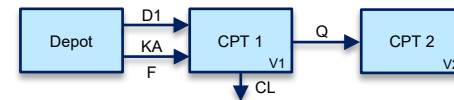
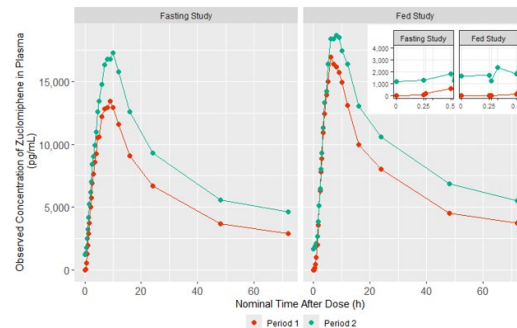
- PK BE study for clomiphene citrate oral tablet using a single-dose, two-way crossover design under fasting and fed conditions in healthy subjects
- Washout period of ~7 times the reported half-life of the RS

Issue

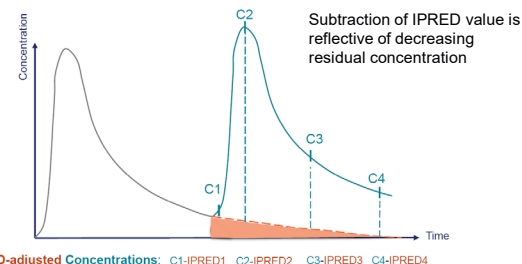
- In Period 2, most subjects had pre-dose concentrations > 5% of the respective C_{max} values^{1,2}
- **Insufficient data for statistical comparison** and BE demonstration after exclusion of data

QCP Approach

- FDA implemented **popPK model-based correction for carryover**
- Study met BE criteria using IPRED-adjusted concentrations



CPT: compartment, F: Apparent bioavailability (F/CL), KA: absorption rate constant, D1: duration for depot CPT, CL: clearance, Q: intercompartmental clearance, V: volume of distribution



Case Study #2: PopPK Prediction of Terminal Elimination Phase (FDA)



Study Design

- PK BE study for NTI drug product using single-dose, four-way, fully-replicate crossover design in healthy subjects under fasting conditions

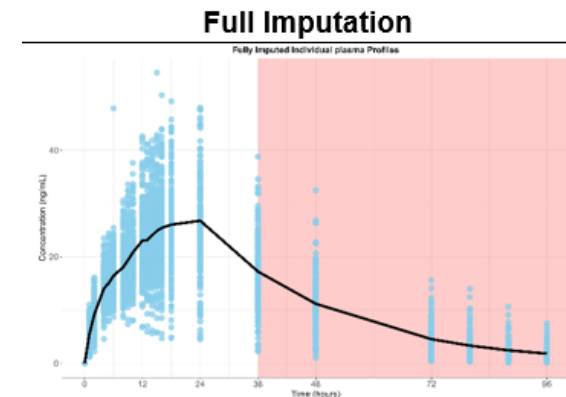
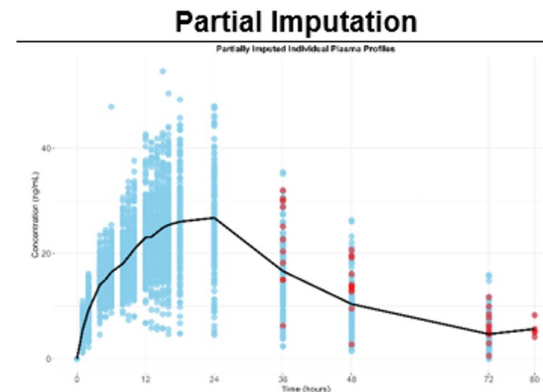
Issue

- Several subjects exhibited **inadequate characterization of the terminal elimination phase**^{1,2}
- Study failed to meet BE criteria for AUCinf after excluding this data

QCP Approach

- FDA implemented **popPK model-based prediction of PK profiles** in terminal elimination phase enabling more reliable estimation of Kel and AUCinf
- Enhances statistical power through BE assessment of more complete datasets

Kel: apparent terminal elimination rate constant, AUCinf: area under the curve extrapolated to infinity



Case Study #3: PopPK Modeling to Address Missing Data from Study Interruption



Study Design

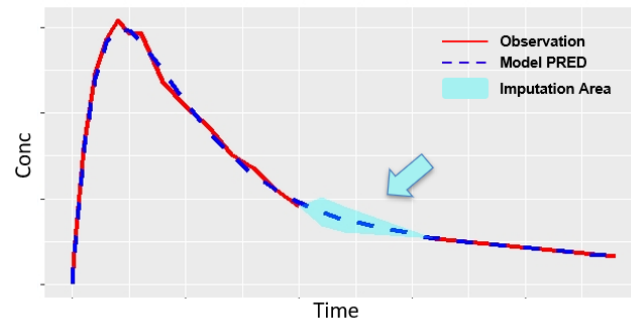
- PK BE study for LAI product using single-dose, parallel design

Issue

- PK data was not collected from a large number of subjects during part of the study due to study interruption

QCP Approach

- Applicant used **popPK modeling to impute missing data**
- BE assessment with imputed data was used for BE demonstration



Simulated time-concentration profiles for demonstration purpose

- PopPK model was developed from the impacted study
- Data imputation is conducted at an individual level
- Missing points are filled by values estimated from the PopPK model with uncertainties estimated (presented as the imputation area)

Case Study #4: Repeated Crossover Design with Sparse Sampling or MIE BE



Recommended Study Design

- PSG for an oncology drug product recommends a PK BE study using a multiple dose, two-way crossover design in patients already receiving a stable dosing regimen

Issue

- Applicant described challenges with **recruitment in rare disease patient population** and **clinical concerns with multiple blood draws in patients** using replicate crossover designs

Proposed Study Design(s)

- Multiple-dose, **repeated crossover** design (TTRR/RRTT) with **sparse sampling**; or
- **MIE BE** approach using a popPK model developed from a **small number of patients**

QCP Approach

- Simulated VBE trials using popPK model and compared NCA/BE results under various optimized sampling schemes
- MIE BE approach was similar with methods developed under GDUFA research³

Proposed MIE for BE Assessment from GDUFA Research Program³

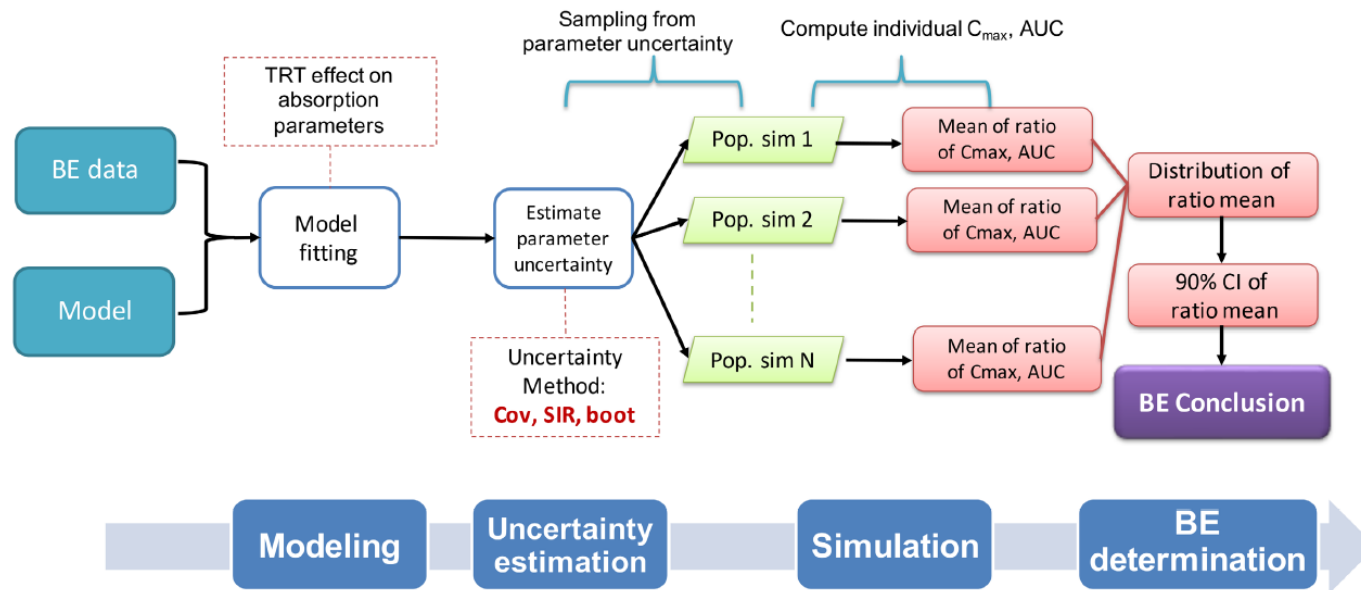


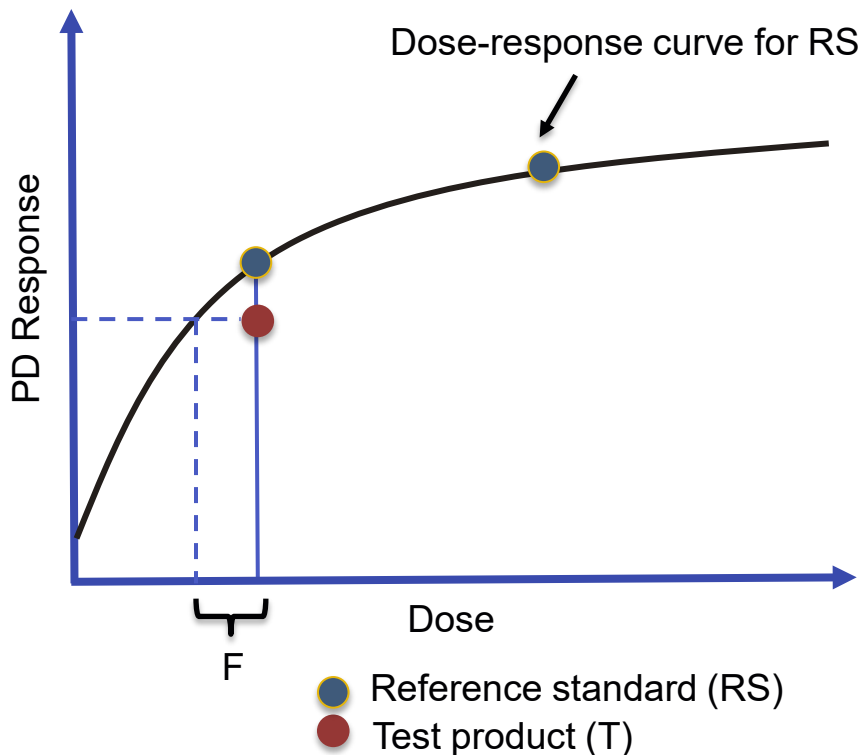
FIGURE 1 Overview of our developed model-integrated evidence approaches for bioequivalence (BE) analysis. The method consists of four steps: (1) model fitting using a pre-defined model for the reference product with additional treatment effect (TRT), sequence effect (SEQ), and period effect (PER) on absorption parameters including bioavailability (F, F is assumed to be 1 for the reference product); (2) uncertainty assessment using covariance matrix (Cov), sampling importance resampling (SIR), or nonparametric bootstrap (boot); (3) simulation for population (i.e., with a large subject number), which can be changed to simulation for a typical subject; and (4) conclusion based on the 90% confidence interval (CI) of the geometric mean ratio obtained from the simulation step.

Regulatory Expectations for PopPK Approaches Supporting BE



Category	Recommendations and Considerations
Study Design:	• Provide sufficient justification for alternative BE approaches that are not recommended in PSG • Provide sufficient justification for sample size(s) used in model development and BE assessment
Modeling Method/Software:	• PopPK using NLME modeling: fixed/random effects, sparse data, less sensitive to study design (Tmax) • Various modeling software: NONMEM, Monolix, Phoenix NLME, and others
Model Development/Validation:	• Pre-specify modeling analysis plan (MAP) • Describe model development (e.g., candidate models, criteria for model improvement, convergence) • Evaluate model adequacy and performance (e.g., GOF, VPCs, individual predictions, other criteria)⁴ • Provided evidence that PopPK model is sensitive to detect formulation differences (e.g., Type I/II error)
Data Analysis/Assessment:	• Pre-specify statistical analysis plan (SAP) including method(s) for handling missing data and BLQ data • Pre-specify methods to address inadequate sampling or inadequate characterization of PK profiles • Evaluate imbalance of missing/imputed data across treatments, missing mechanisms, and impact on BE determination • Assess sensitivity of BE determination under different scenarios (e.g., single-dose vs. steady-state) • Evaluate impact of parameter uncertainty on BE assessment
Virtual BE Trials:	• Address concerns with potential bias in model selection (e.g., conventional model averaging, bootstrap model selection) • Provide sufficient justification for sample size used in virtual BE trials • Specify BE metrics and acceptance criteria for VBE trials [e.g., trials passing (%), distribution of GMRs]

Dose-Scale Analysis for PD BE Study



- Nonlinear dose-response: PD response does not increase proportionally with dose

$$y = E_0 + \frac{E_{max} * Dose * F^i}{ED_{50} + Dose * F^i}$$

(Ref: $i = 0$; Test: $i = 1$)

Where y = Response, Dose = Administered dose, E_0 = Baseline response in the absence of the drug, E_{max} = Fitted maximum drug effect, ED_{50} = Dose required to produce 50% the fitted maximum effect, and i = Treatment indicator (0 = Ref, 1 = Test), with the understanding that $F^0 = 1$ and that F^1 is the relative potency used to evaluate bioequivalence.

- BE of drug products is assessed by estimating relative bioavailability (F) on dose scale, not original scale of PD response
- Suggests equivalence of the amount of drug reaching the site of action
- DSA is recommended in PSGs for demonstrating PD BE of:
 - Albuterol sulfate inhalation products
 - Levalbuterol tartrate inhalation aerosol
 - Orlistat oral capsule

Case Study #5: PD BE Study using DSA for Albuterol Sulfate MDI



BE Recommendations

- Option III: Two in vitro BE studies, one in vivo PK BE study with PK endpoints, and **one PD BE study**

PD BE Study Design

- Single-dose, double-blind, double dummy, randomized, crossover design in subjects with asthma

Concerns

- Sample size was significantly lower** than planned due to study interruption
- Variability** in PD data, **non-positive D-R** relationships, **AQL** data
- Uncertainty** in PD parameter estimates

QCP Approach

- Evaluated adequacy of Emax model (e.g., model development, validation, context of use)
- Demonstrated model is sensitive to detect formulation differences (e.g., Type I/II error)
- Compared model parameter estimates and uncertainty, study power, and BE results to publicly available data
- Evaluated different imputation methods for AQL data
- Provided supportive VBE analysis
- Calculated 90% CI for Frel using two methods

Regulatory Expectations for PD BE Studies Using DSA



Category	Recommendations and Considerations
Study Design:	• Consider recommendations in PSG for study design, population, inclusion/exclusion criteria, methods, and analysis • Provide sufficient justification for alternative approaches that are not in the PSG (e.g., VBE analysis) • Provide sufficient justification that sample size is adequate to develop reliable Emax model and perform DSA
Modeling Method/Software:	• NLME modeling preferred: fixed/random effects, less sensitive to aberrant observations, routinely used in applications • Various modeling software (NONMEM, SAS, R): Results generally consistent with same model structure/parameter settings
Model Development/Validation:	• Describe model development (e.g., candidate models, criteria for model improvement, convergence) • Evaluate model adequacy and performance (e.g., GOF, VPCs, individual predictions, other criteria)⁴ • Evaluate plausibility of PD parameter estimates and compare results to published data if available • Provided evidence that Emax model is sensitive to detect formulation differences (e.g., Type I/II error)
Data Handling:	• Log transformation of PD data should be specified and justified in the protocol • Avoid possibility of negative values (as appropriate) • Pre-specify method(s) for handling dropouts, missing data, and AQL data
Data Analysis/Assessment:	• Evaluate imbalance of missing/imputed data across treatments, missing mechanisms, and impact on BE determination • Investigate non-positive D-R relationships, imbalance between Test product and RS, and impact on model fit • Evaluate impact of uncertainty in PD parameter estimates on BE assessment
Computing 90% CI of F:	• Recommend following the bootstrap procedure in the PSG • Resample original dose-response observations at subject level (typical minimum of 1000 bootstraps) • Alternatively, estimate 90% CI for F directly from the point estimate of F and its SE calculated using NLME modeling • Prespecify modeling software and computation method for 90% CI

NLME: non-linear mixed effects, DSA, dose-scale analysis, D-R: dose-response, AQL: above the quantitation limit, VBE: virtual BE, CI: confidence interval

Summary



- QCP approaches may be utilized to provide scientifically robust alternative BE approaches that preserve data integrity, enhance statistical power, and lead to approval of BE studies that might otherwise fail
- PopPK modeling approaches may be used to address challenges in PK BE studies with incomplete washout, inadequate sampling scheme, and missing data
- NLME modeling (Emax) may be used to address challenges with DSA to assess PD equivalence of albuterol sulfate MDIs

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References and Resources



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5. [Gopalakrishnan, Mathangi et al. "Leveraging Model Integrated Bioequivalence \(MIBE\) to Address Regulatory Concerns and Waive Repeat Bioequivalence Studies-A Case Study with Clopidogrel." Journal of clinical pharmacology vol. 66,1 \(2026\): e70142. doi:10.1002/jcph.70142](#)

Questions?

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